

# Chemotherapy-induced peripheral neuropathy: review for clinical practice\*

## *Neuropatia periférica induzida por quimioterapia: revisão para a prática clínica*

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### ABSTRACT

**BACKGROUND AND OBJECTIVES:** Chemotherapy-induced peripheral neuropathy is the most common neurological syndrome secondary to antineoplastic therapy primarily affecting patients being treated with taxanes and platinum derivatives. Sensory neuropathy is the most frequent type. This study aimed at carrying out a narrative review of the literature on the pathophysiology, clinical manifestations, impact, evaluation, diagnosis treatment and prevention of chemotherapy-induced peripheral neuropathy.

**CONTENTS:** Recent studies have shown association among inflammatory molecules, oxidative stress and development of chemotherapy-induced peripheral neuropathy. Most frequent symptoms are limbs numbness and tingling, with neuropathic pain having significant impact on the functionality of patients submitted to antineoplastic therapy. Several evaluation tools have been tested, being electroneuromyography considered the golden standard for chemotherapy-induced peripheral neuropathy diagnosis. There are different pharmacological strategies for its therapy and prevention.

**CONCLUSION:** It is known that chemotherapy-induced peripheral neuropathy is a frequent syndrome negatively interfering with cancer patients' treatment and quality of life. Different drugs are associated to different risk levels, which show its neurobiological complexity. Prevention, diagnostic and treatment strategies have to greatly evolve to minimize its frequency and severity.

**Keywords:** Cancer, Chemotherapy, Neuropathic pain, Peripheral neuropathy.

### RESUMO

**JUSTIFICATIVA E OBJETIVOS:** A neuropatia periférica induzida por quimioterapia é a síndrome neurológica mais comum secundária à terapêutica antineoplásica e acomete principalmente pacientes que necessitam de tratamento com taxanes e derivados da platina. A neuropatia sensorial é o tipo mais frequente. O objetivo deste estudo foi realizar uma revisão narrativa de literatura sobre a fisiopatologia, manifestações clínicas, impacto, avaliação, diagnóstico, tratamento e prevenção da neuropatia periférica induzida por quimioterapia.

**CONTEÚDO:** Estudos recentes têm demonstrado associação entre moléculas inflamatórias, estresse oxidativo e o desenvolvimento da neuropatia periférica induzida por quimioterapia. Dentre os sintomas, queixas de dormências e formigamentos nos membros são as mais frequentes, sendo a dor neuropática quadro de significativo impacto na funcionalidade dos pacientes em terapia antineoplásica. Diversos instrumentos de avaliação têm sido testados, sendo a electroneuromiografia considerada o padrão ouro para o diagnóstico de neuropatia periférica induzida por quimioterapia. A terapêutica e a sua prevenção contam com diferentes estratégias farmacológicas.

**CONCLUSÃO:** Reconhece-se que a neuropatia periférica induzida por quimioterapia é uma síndrome frequente e que interfere negativamente no tratamento e na qualidade de vida do paciente com câncer. Fármacos diferentes estão associados a graus variáveis de risco, o que mostra sua complexidade neurobiológica. As estratégias de prevenção, diagnóstico e tratamento precisam evoluir sobremaneira no sentido de minimizar a sua ocorrência e a gravidade.

**Descritores:** Câncer, Dor neuropática, Neuropatia periférica, Quimioterapia.

### INTRODUCTION

Recent advances in the development and administration of anticancer therapies have prolonged patients' lives. However, a consequence of this progress is the increased incidence of toxicity-related symptoms affecting nervous system, especially the peripheral nervous system<sup>1</sup>. Chemotherapy-induced peripheral neuropathy (CIPN) is the most common neurological syndrome secondary to anticancer therapy. Sensory neu-

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ropathy is the most frequent type of CIPN, primarily affecting patients treated with taxanes (docetaxel and paclitaxel), platinum derivatives (oxaliplatin, cisplatin and carboplatin), vinca alkaloids (vincristine, vinblastine and vinorelbine), thalidomide and bortezomib<sup>2,3</sup>.

The incidence of CIPN is widely different among studies, with rates from 10% to 100%, especially for therapies involving taxanes and platinum derivatives. This variation is possibly caused by technical differences in identifying CIPN and clinical characteristics of the samples<sup>2</sup>. Although not life threatening, CIPN symptoms, especially neuropathic pain, have negative impact on quality of life (QL) of people and influence adherence to anticancer therapy<sup>3</sup>.

In light of its clinical relevance, this study presents a narrative literature review on CIPN pathophysiology, clinical manifestations, impact, evaluation, diagnosis, management and prevention.

## PATHOPHYSIOLOGY OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

CIPN pathophysiology is in general described as symmetric and bilateral axonopathy where cell bodies of dorsal root ganglia would be involved<sup>4</sup>. Different mechanisms have been proposed for different classes of anticancer agents (Table 1). Platinum derivatives (oxaliplatin, cisplatin and carboplatin) are alkylating agents inhibiting DNA synthesis and replication by mean of cross-bindings established by the platinum complex<sup>4</sup>. These drugs may decrease axonal transportation and, as a consequence, induce sensory neurons apoptosis. Large myelinated fibers are in general the most affected, leading to decreased proprioception and tendon reflexes. Dorsal root ganglia seem to be the primary neural injury site, first affecting lower limb nerves, such as the fibular nerve<sup>5</sup>. In this group of drugs, oxaliplatin may induce two types of neuropathy: one acute and reversible and the other chronic.

Acute neuropathy seems to be caused by oxalate release, which is able to kelate extracellular calcium, interfering with sensory neurons depolarization with consequent membrane hyper-excitability<sup>6</sup>.

Chronic neuropathy has several hypotheses for its development, including the fact that repeated acute neuropathy episodes may lead to chronic neural injuries. In addition, experimental studies show building up of platinum compounds in cell bodies of dorsal root ganglia, resulting in decreased cell metabolism and axonal transportation. There also seem to be mitochondrial injuries with increased oxidative stress, which would induce chronic neu-

ropathy<sup>4</sup>. Baptista-de-Souza et al.<sup>7</sup> have shown in experimental study that oxaliplatin is also able to decrease mRNA expression of the 5HT<sub>2c</sub> receptor in the central nervous system, which could contribute to worsen CIPN neuropathic pain. This would indicate the potential for structural and functional changes in the limbic system caused by oxaliplatin<sup>7</sup>.

Taxanes, especially paclitaxel, are agents promoting the union of microtubules as from tubuline dimers, stabilizing them and preventing their depolymerization. This interferes with dynamic physiological reorganization of microtubules network which is essential for cell vital functions<sup>8</sup>. Taxanes-induced peripheral neuropathy pathophysiology seems to be associated not only to this action mechanism, but also to oxidative stress induced by such drugs, with initial apoptosis of nervous terminations, followed by effects on Schwann cells<sup>9</sup>. Oxygen-reactive species (ORS) seem to play a relevant role in the development and maintenance of paclitaxel-induced pain<sup>10</sup>.

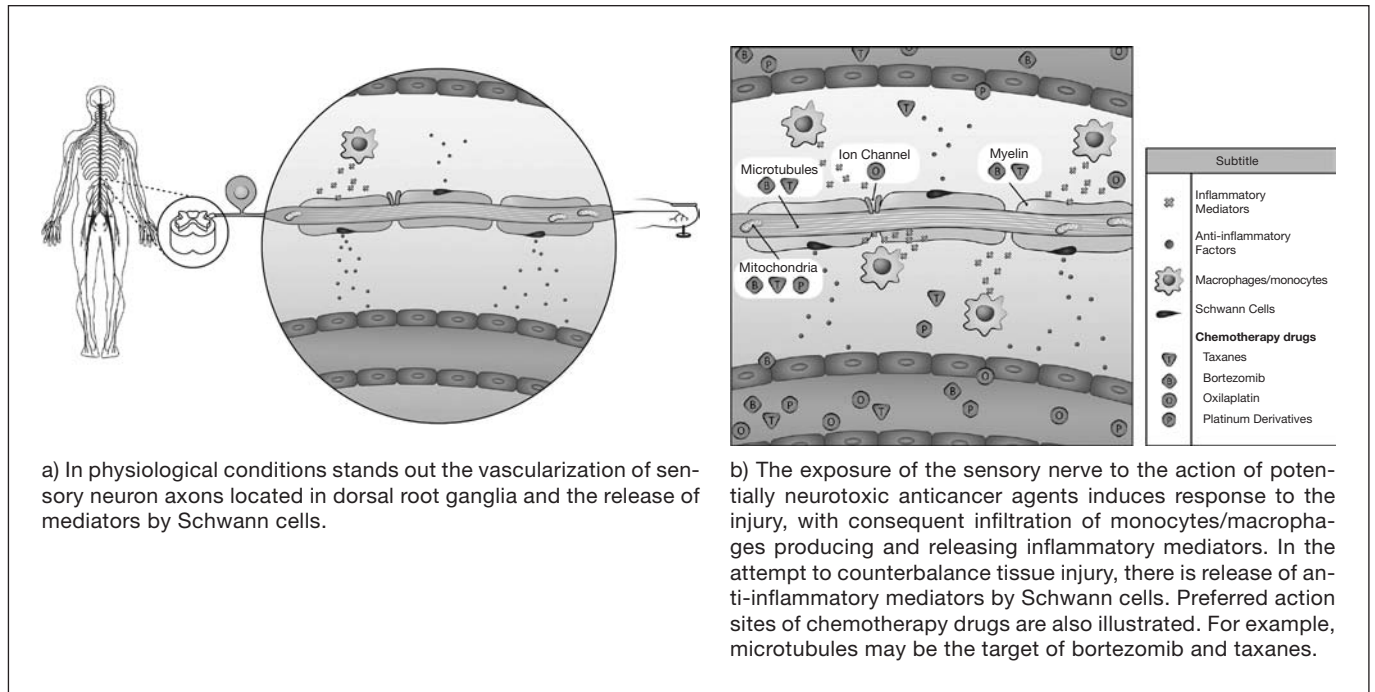
For bortezomib, a proteasome inhibitor, Bruna et al.<sup>11</sup> have described decreased myelinated and non myelinated fibers and the presence of abnormal inclusion bodies in non myelinated axons in rats treated with the drug, which would change pain threshold. An experimental study with rats has shown by electronic microscopy, that there were no significant pathological changes in the morphology of myelin sheath of animals treated with cisplatin, bortezomib and paclitaxel, although there has been decreased nervous conduction velocity<sup>12</sup>. There are evidences that platinum derivatives and taxanes would induce blood vessels endothelial cells apoptosis, with consequent nervous fibers ischemia<sup>13</sup>.

Among pathophysiological CIPN mechanisms, it is currently recognized the role of neuroimmune interaction, since the release of cytokines and chemokines able to trigger peripheral neural injury seems to be a primary mechanism for the development of the syndrome. Experimental studies have shown that, in response to toxic injury triggered by anticancer chemotherapy, there might be neural infiltration of monocytes/macrophages with production of several cytokines (TNF $\alpha$ , IL1 $\beta$ , IL6), chemokines (CX3, CL1, CCL2, CCL3, CCL4, CCL5 and CXCL8) and other inflammatory mediators such as bradykinin, prostaglandins and nitric oxide. Schwann cells may also suffer phenotypic changes and start releasing TNF $\alpha$ , IL1 $\beta$ , IL6 and prostaglandins (PGE2). The same Schwann cells may produce anti-inflammatory factors, such as IL10, in attempt to counterbalance the injury process, thus protecting axons from further injuries (Figure 1)<sup>14</sup>.

Experimental studies have shown the involvement of neurotrophic factors on CIPN pathophysiology. For example, Aloe

**Table 1.** Anticancer agents and respective toxicity mechanisms in the peripheral nervous system

Anticancer agent	Potential mechanisms for triggering peripheral neuropathy
Carboplatin	Decreased axonal transportation
Cisplatin	Induction of sensory neurons apoptosis.
Oxaliplatin	Oxidative stress.
Paclitaxel	Stabilization of microtubules and induction of oxidative stress.
Docetaxel	
Bortezomib	Proteasome inhibition.



**Figure 1.** Role of neuroimmune communication in the pathophysiology of chemotherapy-induced peripheral neuropathy

et al.<sup>15</sup> have observed that there is decrease in NGF (neural growth factor) with cisplatin, which would trigger CIPN. Several studies propose a protective role to BDNF (brain-derived neurotrophic factor) in this syndrome<sup>16</sup>.

Studies investigating the influence of inflammatory mediators on human CIPN are still scarce. A cross-sectional study has evaluated the levels of IL6, IL6R and gp130 in 40 females with breast cancer, being 20 with painful CIPN and 20 without CIPN and who had finished their anticancer therapy between six and 12 months ago. Results have indicated association of such inflammatory mediators and painful CIPN symptoms, as well as worse QL indices<sup>17</sup>.

## CLINICAL MANIFESTATIONS

CIPN incidence and severity are directly related to dose, number of treatment cycles, previous or simultaneous administration of neurotoxic anticancer agents and the type of impaired nervous fiber<sup>13,18</sup>. For example, when cisplatin is used alone, the frequency of neuropathic symptoms is around 50%, while 90 to 100% of females receiving the association of cisplatin and paclitaxel for ovarian cancer may present such symptom. Alcohol abuse and other systemic diseases, such as diabetes, related to higher risk of peripheral neuropathy, predispose the onset of more frequent and severe symptoms, even with the use of low doses of anticancer agents<sup>18</sup>.

CIPN symptoms in general appear in the beginning of the treatment, between the first and third cycles, with severity peak approximately in the third month of therapy<sup>19</sup>. At the end of therapy, differently from other adverse effects, CIPN symptoms may not stop and may even worsen.

Regardless of the type of anticancer agent, symptoms affect lower limbs, upper limbs and orofacial region. Sensory symptoms are far more common than motor or autonomic symptoms. Among autonomic symptoms there are cardiovascular (blood pressure oscillation), gastrointestinal (constipation) and urologic (erection problems and urinary retention) symptoms. Motor symptoms in general manifest as distal weakness (such as feet weakness), gait and balance disorders, and difficulties with fine movements (writing, buttoning clothes, cutting and sewing)<sup>20</sup>. Sensory symptoms are described as bilateral paresthesias, often reported as numbness and tingling in 90% of CIPN cases. In addition, it is common the report of sensation of “wearing a thin sock or glove”, as well as “difficulty to hold things” and to discriminate shape, texture and/or temperature. According to the International Association for the Study of Pain (IASP), neuropathic pain is defined as “pain caused by injury or disease of the somatosensory system”. Neuropathic pain is characterized by the combination of negative symptoms, such as partial or complete loss of sensitivity, as well as positive symptoms which include dysesthesia, paresthesia and pain. Its incidence is 40% of cancer pain patients, being described as “burning” pain and “sensation of shock”, in general involving hands and feet. CIPN may be considered predictor of neuropathic pain, being that CIPN patients have three times more chance of developing neuropathic pain after treatment<sup>18</sup>.

It is worth stressing acute pain induced by paclitaxel (P-APS) and the subsequent risk of developing CIPN. P-APS is characterized by diffuse muscle and joint pain, especially in lower limbs and hips, which starts during the administration of the drug with evolution until one week after the end of the infusion. It is believed that this syndrome might be a red flag for

the need of a prophylactic agent to prevent or minimize the development of taxane-induced CIPN. The severity of P-APS symptoms seems to be directly proportional to the severity of neuropathic symptoms<sup>21</sup>.

CIPN may be dose-limiting. This means that symptoms may evolve to a point in which people can no longer live with them being necessary to decrease anticancer agent dose or even discontinue treatment<sup>22</sup>. In this context, many patients avoid reporting symptoms, delaying CIPN diagnosis by health professionals, which is only possible when the condition is severe and more difficult to handle<sup>21</sup>.

## IMPACT

CIPN has significant impact on QL, directly interfering with daily activities (DA), functionality and behavior of cancer patients<sup>23</sup>. Verbalization of frustration feelings is common as a consequence of social role impairment, of distress due to functional skills changes, in addition to dismay and loss of objectives due to the need to give up some activities<sup>24</sup>. A study has investigated 240 females with breast cancer and CIPN, observing frequent reports of difficulties to drive, to notice texture and temperature differences, to walk on high heels, to button a blouse, to comb their hair or even to cook<sup>23</sup>.

In addition, patients developing neuropathic pain need to come twice as much to health services, need further care and a larger number of drugs as compared to those not developing painful CIPN<sup>18</sup>.

A cross-sectional study has evaluated 706 patients with regard to the influence of CIPN in the development of mental and sleep disorders after the fourth week of potentially neurotoxic anticancer treatment. The worst CIPN severity, the highest the frequency of anxiety, depression and sleep disorders, which were worsened by neuropathic pain<sup>24</sup>. Cognitive impairment, non-adherence to treatment and loss of self-care ability

are also described.

Effects on motility and balance up to 2.5 years after treatment are reported, being related to clinical decay of the elderly who received chemotherapy. Patients under potentially neurotoxic chemotherapy are at higher risk for falls, which increases at every chemotherapy cycle, especially in patients receiving paclitaxel as compared to those receiving platinum derivatives<sup>25</sup>.

## DIAGNOSIS AND EVALUATION OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY

A lot has been discussed about diagnostic and evaluation methods for CIPN severity, but there is still no consensus about which would be the best strategy for the clinical practice<sup>25</sup>. As a consequence, studies on CIPN prevention and management have been impaired by the absence of a simple, clinically useful, psychometrically valid tool in a universally known language to oncology and which could be implemented by different health professionals taking care of this population<sup>26</sup>. The golden standard for CIPN evaluation is electroneuromyography (ENMG), method able to detect nervous behavior changes, especially of myelinated fibers, defining the neuropathic involvement<sup>27</sup>. ENMG more commonly shows decrease or absence of sensory potentials amplitude, especially in the sural nerve. Nervous conduction velocity may also be decreased<sup>28</sup>. However, conventional ENMG does not detect neuropathy of thin fibers and may not identify cases of CIPN restricted to them, which in general course only with pain. There are other limiting factors, such as the fact of being an uncomfortable and high cost exam performed by clinical neurophysiology specialists<sup>27</sup>.

A Medline literature search using descriptors “CIPN” (chemotherapy-induced peripheral neuropathy), “evaluation” and “diagnosis” has identified tools that are being used in the clinical practice (Table 2). Each one has advantages and disadvantages

**Table 2.** Studies of evaluation and diagnosis of chemotherapy-induced peripheral neuropathy using different clinical tools

Authors	Origin	Type of study	Evaluated people	Tools
Simão et al. <sup>30</sup>	Brazil	Cross-sectional	117	MSW, QNIA, ECOG
Hershman et al. <sup>36</sup>	USA	Clinical trial	409	FACT-Taxane NTX, NCI – CTC
Reeves et al. <sup>21</sup>	USA	Longitudinal	85	EORTC- QLQ-CIPN 20
Cavaletti et al. <sup>3</sup>	Italy	Longitudinal	450	TNSc, NCI-CTC 2.0
Simão et al. <sup>25</sup>	Brazil	Review	-	ENMG, ECN, TNS, QNIA, FACT/GOG-NTX & PNQ
Toftthagen, McAllister & McMillanet al. <sup>40</sup>	USA	Validation	167	CIPNAT
Hershman et al. <sup>39</sup>	USA	Cross-sectional	50	QST, FACT/GOG-NTX
Cavaletti et al. <sup>26</sup>	Italy	Review	-	NCI-CTC, ECOG, FACT/GOG-NTX, FACT-Taxane, PNS, Oxaliplatin Scale, PNQ, EORTC- QLQ-CIPN 20
Wilson et al. <sup>27</sup>	USA	Clinical trial	32	ECN, EMG
Loprinzi et al. <sup>33</sup>	USA	Clinical trial	353	EORTC- QLQ-CIPN 20, NCI-CTC
Smith et al. <sup>35</sup>	USA	Clinical trial	231	FACT/GOG-NTX, NCI- CTC

MSW = Semmes-Weinstein monofilaments, QNIA =Anticancer agents-induced neurotoxicity questionnaire and ECOG = Eastern Cooperative Oncology Group Performance Scale; FACT-Taxane = Functional Assessment Cancer Therapy – Taxanes; NCI-CTC = National Cancer Institute Common Toxicity Criteria; EORTC- QLQ-CIPN 20 = European Organization for Research and Treatment of Cancer Quality of Life Questionnaire CIPN 20-item; TNSc = Total neuropathy score clinical version; ENMG =Electroneuromyography, ECN = Nervous conduction study, TNS = Total neuropathy score, FACT/GOG- NTx = Functional Assessment Cancer Therapy/Gynecology Group – Neurotoxicity, PNQ =Patient Neurotoxicity Questionnaire; CIPNAT = Chemotherapy-Induced Peripheral Neuropathy Assessment Tool;QST = Quantitative Sensory testing.

related to applicability, reliability and association to other clinical parameters such as QL<sup>26</sup>. Recently, the CI-PeriNoms Group, made up of 46 research centers of different countries, has been dedicated to establishing the validity and reliability of different CIPN measurement tools. According to their conclusion, available scales have highly diverting reliability and there are gaps, especially in determining the severity of CIPN symptoms<sup>29</sup>. In Brazil, investigators are studying the use of Semmes-Weinstein Monofilaments (MSW) and the Anticancer Agents-Induced Neurotoxicity Questionnaire (QNIA) to evaluate CIPN. QNIA has shown high reliability, being clearly understood by respondents. By means of a cross-sectional study, QNIA and MSW were applied to 87 people in potentially neurotoxic anticancer treatment and to 30 healthy controls. There have been significant differences between groups in all evaluated items, as well as good matching between tools. MSW were able to detect subclinical CIPN presentations<sup>30</sup>.

## MANAGEMENT AND PREVENTION

Aiming at preventing CIPN, different substances are being studied such as vitamin E, aminophosphatine, glutathione, adrenocorticotrophic hormone analogs (ACTH) and diethylciticarbamate. To date, the efficacy of these approaches is not clearly defined. A Cochrane review on interventions to prevent cisplatin-induced neuropathy has concluded that data are insufficient to prove the efficacy of any studied agent<sup>31</sup>.

The role of calcium and magnesium infusion to prevent oxaliplatin-induced CIPN in colorectal cancer patients was evaluated in meta-analysis involving four prospective and three retrospective studies with 1,170 patients. Among them, 892 have received calcium and magnesium infusions (Ca<sup>++</sup>/Mg<sup>++</sup>) and 368 constituted the control group. The incidence of acute neurotoxicity level 3 was lower in the group receiving calcium and magnesium (OR=0.26; CI95%=0.11-0.62; p=0.0002). Cumulative and late toxicity level 3 rates were also lower in the group receiving ion infusions (OR=0.42; CI95% 0.26-0.65; p=0.0001; OR=0.60; CI95% 0.39-0.92; p=0.02, respectively). The difference in the number of oxaliplatin cycles between groups was also significant, indicating better tolerance to treatment by the experimental group. There were no differences in progression-free survival, in global survival or response rate, showing that the administration of calcium and magnesium has not decreased the efficacy of chemotherapy<sup>32</sup>.

However, the study N08CB denies such results: 353 patients receiving adjuvant oxaliplatin for colon cancer were randomized in three arms: intravenous Ca<sup>++</sup>/Mg<sup>++</sup> (IV), 1g calcium gluconate, 1g magnesium sulfate before and after oxaliplatin; placebo before and after oxaliplatin, and the arm receiving IV Ca<sup>++</sup>/Mg<sup>++</sup> before oxaliplatin and placebo after. Primary outcome was cumulative neurotoxicity. There has been no benefit with ions administration, being that cumulative neurotoxicity, acute neurotoxicity and chemotherapy discontinuation rates were similar for all groups<sup>33</sup>.

The possible benefit of venlafaxine was suggested in a small placebo-controlled study with 48 patients with oxaliplatin-

-induced acute neuropathy. The group receiving 50mg venlafaxine 1h before oxaliplatin infusion, followed by 37.5mg twice a day from the second to the 11<sup>th</sup> day, had acute symptoms relief as compared to the group receiving placebo (31 versus 5%). Even three months after treatment, less patients had neurotoxicity symptoms in the venlafaxine group (6 versus 39%). Although promising, these data need confirmation by more robust studies<sup>34</sup>.

The first large phase III study describing an effective intervention for CIPN was recently published. In the double-blind placebo-controlled study (CALBG 170601) involving 231 patients with CIPN induced by taxanes or oxaliplatin, the efficacy of duloxetine was evaluated. Patients received one tablet (30mg) per day during one week and then 2 tablets (60mg) per day for four weeks. The National Cancer Institute-Common Terminology Criteria for Adverse Effects (NCI-CTCAE) was used to classify the level of painful CIPN. This is a subjective scale which evaluates adverse events related to toxicity including peripheral, sensory and motor neuropathy, dysesthesia, paresthesias, as well as neuralgias, with scores from 1 to 5 according to symptoms severity.

With regard to pain and QL, the following tools were used: Short Form of the Brief Pain Inventory (BPI-SF), which measures pain intensity and interference, Functional Assessment of Cancer Therapy/Gynecologic Oncology Group-Neurotoxicity (FACT/GOG-Ntx) which evaluates QL and neurotoxicity, in addition to the European Organization for Research and Treatment of Cancer (EORTC) and the Quality of Life Questionnaire 30 (QLQ-30) used to evaluate QL. As compared to placebo, the relative risk of 30% less in pain with duloxetine was 1.96 (CI95%=1.15-3.35) and of 50% less pain was 2.43 (CI95%=1.11-5.30). Patients treated with oxaliplatin had higher benefit as compared to those treated with taxanes. Duloxetine was also associated to functional and QL improvement<sup>35</sup>. A criticism to the study relates to tools to evaluate the level of neuropathy, which were based only on subjective judgment.

A different perspective for CIPN management would be Alcar, an L-carnitine ester which helps energetic metabolism and may be endogenously produced or acquired by diet<sup>22</sup>. Preliminary studies showed that Alcar would probably not influence ovarian cancer treatment and could have a neuroprotecting effect by different mechanisms, including increased NGF receptor expression<sup>22</sup>. The Southwest Oncology Group (SWOG) S0715 study has contradicted initial optimism after evaluating the role of Alcar in preventing CIPN in 409 patients receiving taxanes during adjuvant breast cancer therapy. With regard to control group, there has been a trend to worsening neurological symptoms in the intervention group after 24 weeks of follow-up<sup>36</sup>. A randomized placebo-controlled study has evaluated the efficacy of baclofen (10mg), amitriptyline (40mg) and ketamine (20mg) in a lecithin in organogel (BAK-OLP) versus placebo (OLP) to treat CIPN during 4 weeks in 208 patients. This topic gel provided a slight improvement in symptoms as compared to the placebo group, both in sensory and motor symptoms. There have been no reports of undesirable local toxic effects with BAK-OLP or of systemic toxicity effects<sup>37</sup>.

In summary, from pharmacological viewpoint, there are no consistent evidences about the efficacy of CIPN prevention strategies. Duloxetine is the best available evidence to treat CIPN-related symptoms. Given the efficacy of neuropathic pain management, tricyclic antidepressants (nortriptyline, amitriptyline) and gabapentin may be considered in the context of painful CIPN<sup>38</sup>. Even without scientific evidences, non-pharmacological strategies are widely employed for CIPN symptoms, including physiotherapy, acupuncture, physical activity, massages and occupational therapy, in addition to educative interventions aiming at encouraging patients and their families to be careful with symptoms and to plan home environment<sup>23</sup>.

## CONCLUSION

It is known that CIPN is a frequent problem negatively interfering with anticancer therapy. Different drugs are associated to variable risk levels, which shows CIPN neurobiological complexity. Prevention, diagnosis and management strategies still have to evolve to minimize CIPN incidence and severity. Patients should be informed about the limitations of scientific evidences for CIPN prevention and management, as well as about their potential risks, benefits and costs.

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